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A BRIEF SUMMARY OF THE INVENTION

Summary, Objects and Advantages

A conceptual discovery. The qualitative nature of an elementary mental state is primarily determined by the constitutively expressed locus-specific proteins of brain locus evoking it (K1 proteins).

Methods. The invention provides methods for identifying brain loci, and of constitutively expressed proteins specific to said brain loci, the deactivation of either said loci, or said proteins, selectively impairs the otherwise normal behavioral response to said stimuli.

Advantages. Identified said brain loci and said proteins provide the most selective targets for modulating the correlated elementary mental states, thus increasing the effectiveness, and decreasing the side-effects, of medical intervention.

~~**BRIEF DECRIPTION OF THE SEVERAL VIEWES OF THE DRAWINGS**~~

~~1/5 — Prior art: The *tabula rasa* doctrine — The central misconception~~

~~2/5 — Primary and secondary modality-specific cortical areas~~

~~3/5 — Flowchart of overall identification method~~

~~4/5 — A flowchart of a method for identifying L in the mouseDETAOLED~~

DETAILED DESCRIPTION OF THE INVENTION

Background – Description of prior art

A. Some fundamental conceptual issues

A1 *The search for neural correlates of mental states.* Mental states, though private, may be investigated through their physical manifestations in the brain. Hence the current search for identifying brain correlates of mental states (Chalmers 2001). However, the computer model of the brain implies that no mental state can have a unique brain correlate. To date, none have been found. It turns out that the implication of the computer model is empirically false, and that the technique necessary for identifying the brain correlates have been available for over a decade. The following briefly reviews basic conceptions that underlie present-day views about the relation of the mind to the brain.

A2 *The central tenet underlying present-day notions about the nature of the mind.* The great majority of neuroscientists take it for granted that sensations are received in the central nervous system (CNS) from the peripheral nervous system (PNS). This assumption is a manifestation of the *tabula rasa* doctrine that was introduced by John Locke (1775/1975). It denies that mental states are innate, or evoked in the CNS ~~(Fig. 1A)~~. Locke followed Democritus, Galileo, and Newton in partitioning what is perceived into properties such as size and shape, which were attributed to the external world, and properties such as sound and color, which were deemed to be subjective. This made Locke's version of the *tabula rasa* doctrine dualistic.

A3 *Physicalism.*

A3.1 Physicalism is a non-dualistic version of the *tabula rasa* doctrine. Physicalism removes the dualistic element of the *tabula rasa* doctrine by considering properties such as sound and color to be properties of the external world, and thus objective. Neuroscientists who subscribe to Physicalism take sound, for example, to be a property of air vibration (Kelley 1991). Similarly, color is taken to be a property of electromagnetic radiation ~~(Fig. 1B)~~.

E. Submodality-specific areas of the cerebral cortex

E1 *Modality-specific areas of the cerebral cortex.* Each sensory modality is processed in a separate, spatially contiguous cortical area. For example, modality-specific thalamic nuclei for olfaction project their primary output to the orbitofrontal cortex, making that cortical area modality-specific for olfaction. The initial target for the thalamic projection is the *primary* modality-specific cortical area. The modality-specific information from the thalamus relates to different submodalities. Each submodality is then processed in distinct *secondary* areas within each modality-specific cortical area. The output of this *unimodal* information is then projected to association areas, which are not modality-specific ~~(Fig. 2A)~~.

E2 *Primary and secondary areas in the somatosensory cortex.* Conventionally, Brodmann areas (BAs) 3a, 3b, 1, and 2 are collectively called the primary somatosensory cortex. Primary sensory cortex is one that receives its primary input from the corresponding modality-specific thalamic nuclei. By this criterion BA3a and BA3b are primary sensory cortical area, while BA1 and BA2 are secondary sensory cortical areas. More precisely, BA1 receives its main input from BA3b, and is submodality-specific for light touch (input from rapidly adapting mechanoreceptors). BA2 integrates input from BA3b about pressure (from slowly adapting mechanoreceptors with information about light touch from BA1 ~~(Fig. 2B)~~.

E3 *Columns in submodality-specific cortical areas.* The column is a unit of elementary function in the cerebral cortex. The column also has been identified as a unit of subjective sensation in several submodality-specific cortical areas. In the visual cortex, these areas include columns in V5 for the sensation of direction of movement, columns in the anterior inferotemporal cortex for basic visual forms. In the somatosensory cortex, the direct electrical stimulation of BA1 in normal awake human subjects produce the sensation of light touch in the corresponding part of the body surface (Penfield 1950). Mountcastle (1957) demonstrated its columnar

O. Overview of the identification method ~~(Fig. 3)~~

O1 *An outline of the identification method.* Behavioral responses to stimuli are correlated first with subjective states, then with preferentially activated brain loci, and finally with constitutively expressed proteins specific to these brain loci, as follows:

O1.1 Correlating behavioral responses with subjective states. Behavioral responses are correlated with JNDs within the same sensory submodality, to stimuli of constant intensity and duration.

O1.2 Correlating behavioral responses with brain loci. Part I. Preferentially activated brain loci are identified in the mouse using 2D-G, in the monkey using voltage sensitive dyes, and in humans using non-invasive brain imaging.

O1.3 Correlating behavioral responses with brain loci. Part II. Brain loci that manifested preferential activation in response to the external stimulus are deactivated. Brain locus whose deactivation selectively impairs the otherwise normal behavioral response to the external stimulus satisfies the correlation criterion. In humans, L' loci can be deactivated by means of transcranial magnetic stimulation at low frequency.

O1.4 Identifying K1 proteins. Part I. Using protein chips to identify L' locus-specific proteins in slices of tissue samples from human brain bank; using persistent stimuli to amplify mRNA transcription of K1 proteins of L loci in mice during their postnatal critical period then using subtractive hybridization to identify these proteins and their human homologues; Using databases to search for locus-specific proteins in identified brain loci

O1.5 Identifying K1 proteins. Part II. Testing that deactivating the function of CELS proteins selectively impairs the otherwise normal behavioral response to stimuli.

P. Methods of identifying brain loci L in experimental animals ~~(Fig. 4)~~

P1 *Considerations relating to the use of experimental animals*

P1.1 The mouse as an experimental subject. The mouse may have about the same number of genes, but only about one-tenth of the brain-specific proteins, as humans. The three association areas (posterior, limbic, and anterior) are where humans differ most from non-human mammals. Additional important differences relate to perception, and some to sensations. The mouse, for example, is colorblind. But monkeys have cortical areas for color homologous to ours (Hadjikhani et al. 1998). The invention relates to identifying shared localized neural function, and then identifying CELS K1 proteins specific to these loci.

P1.2 Innateness and restricted stimulus. The environment of newborn mice should keep their responses uncontaminated by extraneous stimuli. In identifying the correlates of innate fear, for example, conditioned fear cues should be minimized, and the stimulus employed should evoke an innate response, such as abrupt loud noise or smell of cats. If the goal is to identify the correlates of basic taste, then exposure of newborn mice should be limited to one basic taste, and information about other tastes blocked. If the goal is to identify the neural correlates of the sensation of light, it is necessary to exclude elements of the stimulus related to form, depth, and movement (and also of color in experimental animals with color vision).

P1.3 Training. For stimuli types where there is normally no externally observable response, the experimental animals are trained to exhibit stimulus-recognition behavioral response. Correct recognition is reinforced by reward, such as a pellet of food, and incorrect response by punishment, such as non-damaging electric current.

P5 *Identifying brain locus whose inactivation selectively abolishes response R.*

P5.1 Training animals to manifest behavioral response to external stimulus. A new set of animals is partitioned into Group A and Group B. Group A is trained to exhibit behavioral response Rj to stimulus Sj; and Group B is trained to exhibit response Rk to stimulus Sk.

P5.2 Selective deactivation. A brain locus identified as activated in response to the particular external stimulus is then deactivated. The inactivation technique may consist of local surgical lesion, local application of neurotoxin (in non-human primates reversible deactivation would be used, such as local application of lidocaine.

P5.3 Post-deactivation test. Group A mice, with brain loci deactivation in stage O5.2, are then presented with the external stimulus Sj, that normally is followed in them by behavioral response Rj. Lj is that brain locus whose inactivation selectively abolishes behavioral response Rj. Animals in Group B are then subjected to external stimulus Sk. Rk is that brain locus whose deactivation selectively abolishes behavioral response Rk.

Q. Methods for identifying P and P' in the mouse ~~(Fig. 5)~~

Q1 *Outline of the identification of P and P' proteins by use of experimental animals.*

1. Selectively amplify mRNA transcription of K1 proteins
2. Using subtractive hybridization, isolate amplified mRNA/cDNA of K1 proteins.
3. Deactivate function of P by delivering antisense fragments to L brain loci.

Q2 *Contrastive amplification of mRNA transcription.* Mice in their postnatal critical stage would be partitioned into Group A and Group B. Group A is then subjected to persistent stimulus Sj; and Group B is subjected to persistent stimulus Sk.